

The emergence of post-COVID-19 mucormycosis in India: Can we prevent it?

For the last several weeks, the Indian media both newspapers and the TV have been reporting patients who developed mucormycosis (majority rhino-orbital-cerebral mucormycosis (ROCM)), wrongly called as “Black fungus,” within short time of COVID-19 recovery or during the disease itself. The reports have emerged from several states such as Maharashtra, Gujarat, Rajasthan, Madhya Pradesh, Uttar Pradesh, Karnataka, Tamil Nadu, Punjab, Haryana, Himachal Pradesh, Chandigarh, Delhi to name a few and have created an alarming situation for want of an effective treatment and extremely high mortality.

Mucormycosis is an angioinvasive fungus that is usually present in the environment and grows on wet surfaces and dead and decaying vegetable matter. The term “black fungus” being used for mucormycosis is incorrect as the term “black fungus” is used for dematiaceous fungi, which are an entirely different group. Various risk factors for mucormycosis are immunocompromised host, uncontrolled diabetes mellitus especially diabetic ketoacidosis, treatment with glucocorticoids, hematological malignancies, hematopoietic stem cell transplantation, treatment with iron chelating therapies, AIDS, trauma/burns, etc.^[1] Mucormycosis can be rhino-orbital-cerebral, pulmonary, gastrointestinal, and cutaneous.

Among all clinical types, ROCM is easily diagnosed, but mortality may go high due to delay in seeking medical care.^[1] Presently, these cases are being seen in alarming numbers in India in the context of COVID-19. Despite extensive dissection of the sinuses and exenteration of the orbit besides the usual antifungal therapy, mortality rates are reportedly very high.

Most of the reports in lay media have blamed excessive and injudicious use of corticosteroids in patients with COVID-19 who often happen to suffer from uncontrolled diabetes as well. It may be pertinent to mention that corticosteroids are life-saving and millions of patients suffering from SARS-CoV-2 virus infection in the western world (USA, UK, and Europe) have been treated with corticosteroids to control the cytokine storm which, if left uncontrolled, leads to fatal outcomes. Why specifically do we have an alarming surge of ROCM in India versus the rest of the world when the treatment protocols essentially remain the same remains unanswered? Mucor is ubiquitous, all around us in India or the developed world and all individuals breathe them constantly. While no single factor has been found as yet, it is likely that a distinct constellation of factors, some controllable and others uncontrollable in the Indian setting may be responsible for the emerging epidemic of mucormycosis. Uncontrolled diabetes is rampant in India and a majority of patients do not have regular testing of blood sugar levels. Further, due to a tremendous overload of patients in the hospitals, doctors perhaps were not able to test the blood sugar levels of all patients. Moreover, it has been seen that many of these patients were using dexamethasone way beyond the recommended dose of 6.0 mg/day for 5–10 days. An additional factor could be an attempt to control oxygen saturation with excessive corticosteroids while there was an oxygen shortage in the hospitals. As some of the patients who developed diabetes during their COVID-19 sickness were previously not known to have diabetes, it may have been caused by damage to pancreatic

beta cells by the SARS-CoV-2 due to its affinity to the ACE2 receptor and indirectly by damaging smaller blood vessels supplying beta cells. SARS-CoV-2 regulates ferritin, and causes extensive endothelitis, although it has not been studied well in COVID-19-associated Mucormycosis. It is also likely that we have higher load of mucor spores in the indoor and outdoor air in India due to tropical and humid climate.

It is an incontrovertible fact that the ROCM upsurge is being seen in the context of COVID-19 in India. Briefly presented is evidence that in patients with uncontrolled diabetes, a dysfunctional immune system due to SARS-CoV-2 and injudicious use of corticosteroids may be largely responsible for this malady.

1. Role of the innate immune system:

- a. All humans are exposed to airborne fungal spores and other microbes which find their way into the air passages. However, in normal circumstances, these are not allowed to set up infection. We possess highly efficient and potent innate immune mechanisms that provide a front-line defense against any invasion by microbes. We survive because of this defense system. Briefly, the major players in this mechanism are neutrophils (polymorphonuclear cells, PMN) and the macrophages, the cells of the myeloid descent that are produced in the bone marrow and form a major component of the circulating blood. These cells are provided with surface proteins that identify pathogen-associated molecular pattern present on microbes and immediate action is taken in the form of phagocytosis (Macrophages) and release of Oxy free radicals by the neutrophils that destroy the invading microbes.
- b. Patients suffering from COVID-19 have neutrophilia with lymphocytopenia so much so that a high neutrophil and lymphocyte ratio is used as a surrogate for severity of the disease.
- c. Two recent reports have indicated that SARS-CoV-19 virus infection leads to a dysfunctional innate immune system. Thus, patients who have a severe COVID-19 infection may have a compromised or incompetent innate immune system.^[2,3] This phenomenon needs to be confirmed in much larger studies.
- d. In the event, in severe COVID-19, the macrophages present in the airways are likely impaired and not capable of phagocytosing the fungal spores present and thus unable to eliminate the spores and allow them to germinate into hyphae (nonseptate, right-angled ribbon-like filaments of Mucor).
- e. In normal innate immune-competent individuals, the hyphae are dealt with by mature neutrophils which release a burst of oxy free radicals to destroy the hyphae. In the COVID-19, while there is neutrophilia, there is a premature release of these cells from the bone marrow. Unlike lymphocytes that mature in regional lymph nodes, neutrophils and other cells of myeloid origin have to mature in the bone marrow. Thus, the available neutrophils to fight the fungal hyphae are immature and not competent to destroy these. CD 10+ is a marker for the maturity of the neutrophils and can be tested in the blood^[4] and possibly in fresh tissue samples.

2. **Role of corticosteroids in COVID-19:** Corticosteroids use was recommended by the WHO in severe to critical patients as a life-saving measure based on its safety profile in short-term use. While there is no difference in the efficacy of a variety of corticosteroids, dexamethasone is preferred.^[5]

Regardless of the preexisting diabetes, it is recommended to monitor blood glucose and in patients with diabetes, corticosteroids should be used for controlling the cytokine storm under insulin control. It was expected that physicians would be aware of the local endemic microbiological flora.^[6] Excessive and injudicious use of corticosteroids in patients with diabetes is believed to be responsible for the upsurge of ROCM by most. An exhaustive review on the effect of corticosteroids on innate immunity in the context of airway epithelial cell lining the subject is available.^[7] Briefly, inhalational corticosteroids are often used in major pulmonary diseases namely COPD and asthma to prevent exacerbations that are prompted by inhalation of microbes, particulate matter, smoke, etc. Normal innate immune mechanisms of airway epithelial cells do not allow these microbes to set up base in the airways. However, glucocorticoids inhibit dendritic cell (DC) maturation resulting in attenuated DC activity.^[8] They also interfere with T cell signaling resulting in dampened T cell activity. Expression of several kinases involved in T cell signaling is also modulated.^[9] Corticosteroids reduce the inflammatory cytokines (IL-1, TNF α , IFN α/β , and granulocyte-macrophage colony-stimulating factor, GM-CSF), chemokines, and the inflammatory enzymes (iNOS, and COX2).^[7] Inducible nitric oxide synthase plays an important role in generation of free radicals and its reduced expression may contribute to a dysfunctional immune system incapable of dealing with the fungal hyphae. Although number of neutrophils is increased, there is inhibition of neutrophil adhesion to endothelial cells and hence decreased trafficking. Glucocorticoids adversely affect macrophage function by decreasing absolute counts, decreased trafficking and phagocytosis function, and decreased expression of MHC Class II molecules. This in turn increases susceptibility to infection. The role of corticosteroids may thus be like a double-edged sword which calls for their highly judicious use in order to prevent this complication. In a paper under publication, it was seen that only 36.7% patients were using appropriately (AC).

3. **Role of uncontrolled diabetes:** Without a doubt uncontrolled diabetes is a major risk factor in the current spurt of mucormycosis in COVID-19 patients. Autopsy studies have indicated that compared to the patients who died from H1N1 influenza, patients with COVID-19 have shown widespread endothelial damage.^[10,11]

Endothelial adhesion and penetration are critical early step for mucormycosis.^[11]

Hyperglycemia acidic state induce the endothelial receptor glucose regulated protein (GRP 78) and the mucorales receptor protein homologs (CotH) create "perfect storm" for increased adhesion and penetration of mucorales.^[12] Mucor is an angioinvasive fungus and its interaction with vascular endothelial cells is critical to its invasion, rapid spread, and thrombosis and tissue necrosis leading ultimately to tissue gangrene that looks black and hence the name, black fungus. Uncontrolled diabetes with ketoacidosis enhances the adhesion of mucor hyphae to the extracellular matrix followed by an invasion of the endothelial cell lining of blood vessels. Baldin and Abrams have recently reviewed at length the pathomechanisms of mucormycosis and the role of uncontrolled diabetes and diabetic ketoacidosis among other factors.^[11]

4. **What are the controllable factors?**

a. While diabetes is eminently controllable before the onset of COVID-19, it quickly gets out of control on exposure to steroids. Maintaining strict control of diabetes during the admission and later cannot be emphasized enough. Likewise, judicious use of corticosteroids cannot be

overemphasized both for its adverse effect on adaptive immunity and the control of diabetes.

b. **Controlling the environmental factors:** While the presence of fungal spores cannot be helped in the environment, all efforts may be initiated to use filters including HEPA if possible in the ICUs since we know that once these spores enter the patient's airway system, not much can be done to prevent the sprouting of the spores and invasion by the mucor hyphae. We are not aware if as yet there is any known safe antifungal agent to prevent the mucormycosis. We do not recommend the use of prophylactic amphotericin-B given its known renal toxicity.

c. **Source of fungus:** We need to find the exact source of the mucor in the ICUs. Is it in the air, humidifiers, catheters, tubing ventilators, or the masks? Humidifier bottled water is continuously agitated due to passage of oxygen. Even if we believe that humidifier water is contaminated, mucorales will not be able to produce spores in agitated state. It must be noted that spores are the inoculating medium and not the hyphae. In screening of oxygen pipelines, oxygen, and humidifier bottled water from three hospitals, only one dematiaceous fungus colony was found from humidifier water (AC).

d. **Is it mucor or aspergillus:** We do not have as yet information whether all cases of ROCM are caused by mucor or other angioinvasive fungi such as *Aspergillus fumigatus* may be have been responsible for at least some of the cases as both produce identical clinical picture. This should call for microbiological and histopathological sampling wherever possible as the prognosis is better in *A. fumigatus* infection compared to mucor and treatment is different for the two fungi.^[13]

5. **Action plan:**

a. ROCM has been declared a notifiable disease by the Government of India that will help to collect and collate nationwide data from all across the country. However, to find out the exact reasons for its exclusive occurrence in the Indian context can be found only through root cause analysis. Thus, an exhaustive set of information should be sought from all care centers which will help in zeroing on the causative factor/factors to prevent this highly undesirable complication.

b. Data from all such ROCM-affected patients from across the country may be collected to look for any regional distribution, age, gender, underlying disease specificities, use of corticosteroids with dosage and duration of hospital admission, type of ICU, e.g., makeshift oxygen bed/ICU or the institutional ICU, the use of medical-grade oxygen or the commercial oxygen, type of water used in humidifiers, and how frequently it is changed. Specifically, look for any items that may be reused. Random air samples may be collected from the areas where the patients are treated.

6. **SOP:** While complexity of COVID-19 dictates that the physicians treating patients have to take decisions to institute a variety of interventions, general guidelines for the use and against the use of certain therapies should ensure fairly uniform evidence-based quality-controlled interventions. Self-use of medication and interventions may be strictly banned. Minimum set of standards may be developed for all the agencies caring for these patients. The guidelines may be updated on a daily basis and strict compliance with these may be ensured through nodal officers. These should be available to all the stakeholders through an open-access government website. Moreover, standard operating procedures are required to be developed

for all settings of patient care, with clear recommendations regarding ophthalmic and nasal screening along with development of tools to monitor compliance.

7. **Early warning symptoms:** patients who are discharged from the hospital care may be given a set of early warning symptoms that should not be ignored and contact numbers of preferably ENT surgeons be provided for an emergency online consultation.
8. Academic institutions should be encouraged to carry out basic and applied research in all aspects of "Post-COVID-19 mucormycosis" in India.

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